



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61J 31/435, 31/445, 31/24</b> <b>A61J 31/22, 31/23, 31/16</b> <b>A61J 31/075</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 94/08550</b>  <b>(43) International Publication Date:</b> 28 April 1994 (28.04.94)
<b>(21) International Application Number:</b> PCT/US93/08957 <b>(22) International Filing Date:</b> 21 September 1993 (21.09.93)  <b>(30) Priority data:</b> 07/955,013                      9 October 1992 (09.10.92)                      US 9306937.5                      2 April 1993 (02.04.93)                      GB  <b>(71) Applicant (for all designated States except US):</b> THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> CLOSE, Peter [GB/GB]; Flat #1, Holly Lodge, 218 Windsor Lane, Burnham, Berkshire SL1 7HN (GB). RUSSELL, Carmelita, Macklin [US/US]; 607 Vincennes Court, Cincinnati, OH 45231 (US). UPSON, James, Grigg [US/US]; 11268 Springfield Pike, Cincinnati, OH 45246 (US).		<b>(74) Agents:</b> REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45202 (US).  <b>(81) Designated States:</b> AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> ANAESTHETIC COMPOSITIONS  <b>(57) Abstract</b>  Anaesthetic compositions comprising a pharmaceutically-acceptable local anaesthetic, a physiological cooling agent and a carrier. The compositions display a reduction in the feeling of numbness associated with anaesthetics and enhanced consumer perception of pain relief.		

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## Anaesthetic Compositions

### Field of the Invention

This invention relates to anaesthetic compositions for application to or consumption by the human body. In particular, it relates to anaesthetic compositions which exhibit effective anaesthetic activity in the throat while at the same time reduce the feeling of numbness in the mouth and throat associated with use of anaesthetics.

### Background of the Invention

Local anaesthetics are well known in the art for the treatment of sore throats. They have been incorporated into pharmaceutical compositions and administered in the form of sprays, gargles, lozenges and tablets.

Local anaesthetics reduce pain by impairing the generation and conduction of the nerve impulses by slowing depolarisation. This results from blocking of the large transient increase in permeability of the cell membrane to sodium ions that follows initial depolarisation of the membrane. Local anaesthetics also reduce the permeability of the resting axon to potassium and to sodium ions. A widely used local anaesthetic is lignocaine. The site of action of lignocaine is on a specific receptor site

in the sodium channel. CH-A-657,777 and CH-A-643,144 disclose compositions containing lignocaine and antacids for the treatment of oesophagitis. Another widely used local anaesthetic is benzocaine. Both benzocaine and lignocaine have been used as anaesthetics in lozenge and spray forms of dosage.

AU-A-8,943,891 discloses a solid dose form, preferably a lozenge, for appetite suppression containing benzocaine or lignocaine and a peppermint flavour. Administration of an anaesthetic to the taste receptors in the mouth by slow dissolution of chewing reduces nervous transmission to the hypothalamus and suppresses the appetite control centre.

EP-A-0,431,376 discloses a lozenge for sustained release treatment of sore throats comprising hydrogenated isomaltulose and an active ingredient which can be an anaesthetic such as benzocaine. Similarly, US-A-4,917,894 discloses an oral anaesthetic composition in the form of a liquid or a lozenge preferably comprising dyclonine and an anaesthetic selected from hexylresorcinol and benzocaine.

While these anaesthetic-containing formulations produce sufficient pain relief in the throat there is, however, often an undesirable numb feeling in the mouth and throat following administration. This is particularly noticeable when the compositions are administered in the form of lozenges or tablets.

It would be desirable to provide anaesthetic compositions which while providing effective sore throat pain relief, also reduce the feeling of numbness associated with anaesthetics. Although there are many examples in the art for providing compositions with anaesthetic activity, there has apparently been no disclosure of an anaesthetic composition which also reduces the feeling of numbness associated with anaesthesia and enhances the perceived feeling of pain relief.

The present inventors have found that by incorporating a cooling agent into a composition along with the anaesthetic the desired benefits can be achieved.

Compositions of various types have incorporated within them components which provide a cooling sensation to mucosal membranes and/or to skin. Such compositions include toothpastes, mouthwashes, perfumes, lotions, shaving cream, post shaving preparations, shampoos, antiperspirants, deodorants, beverages, chewing gum, tobacco products, and pharmaceutical products among many others.

It is well established that the "cooling" effect of menthol is a physiological effect due to the direct action of menthol on the nerve endings of the human body responsive for the detection of hot or cold and is not due to latent heat of evaporation. It is believed that the menthol acts as a direct stimulus on the cold receptors at the nerve endings which in turn stimulate the central nervous system.

Several other compounds have been reported in the technical literature as having an odour or flavour similar to menthol and from time to time have been proposed as flavourants or odourants in a variety of topical and ingestible compositions. For example, JP-A-39-19627 reports that 3-hydroxymethyl p-menthane (menthyl carbinol) has a flavour closely resembling that of 1-menthol and suggests its use as a flavourant in confectionary, chewing gum and tobacco. In CH-A-484,032, certain saccharide esters of menthol are proposed as additive to tobacco. In FR-A-1,572,332, N,N-Dimethyl 2-ethylbutanamide is reported as having a minty odour and refreshing effect, and the minty odour of N,N-diethyl 2,2-dimethylpropanamide is referred to. A similar effect is reported for N,N-diethyl 2-ethylbutanamide in *Berichte* 39, 1223, (1908). A minty odour has also been reported for 2,4,6-trimethylheptan-4-ol and 2,4,6-trimethyl hept-2-en-4-ol in *Parfums-Cosmetiques-Savons*, May 1956, pp. 17-20. The cooling effect of menthol and other related terpene alcohols and their derivatives has also been studied and reported in *Koryo*, 95, (1970), pp. 39-43. 2,3-p-menthane diol has also been reported as having a sharp cooling taste (*Beilstein, Handbuch der Organischen Chemie*, 4th Ed. (1923) Vol. 6, p. 744).

Carboxamides have also been disclosed for use in a variety of compositions. Two patents describing such materials and compositions

are US-A-4,136,163, January 23, 1979 to Watson et al. and US-A-4,230,688, October 28, 1980 to Rowsell et al.

EP-B-0,080,148 discloses the physiological cooling agent 3-l-menthoxy propan-1,2-diol (MPD), which is a monoglycerin derivative of l-menthol.

Although the use of coolants in a wide variety of compositions is well known in the art, there is no art to suggest, however, that cooling agents have been used alongside anaesthetics within compositions to reduce the feeling of numbness associated with anaesthetics and to increase consumer-acceptability.

Accordingly, the present invention provides an anaesthetic composition having enhanced consumer perception of pain relief while at the same reducing the unpleasant feeling of numbness associated with anaesthetics.

#### Summary of the Invention

According to one aspect of the present invention there is provided a composition for application to or consumption by the human body comprising:

- i) from about 0.01 % to about 1 % by weight of composition of a pharmaceutically-acceptable local anaesthetic,
- ii) from about 0.01 % to about 1 % by weight of composition of a physiological cooling agent, and,
- iii) a carrier,

wherein the physiological cooling agent comprises one or more cooling agents having a threshold cooling value of less than about 100 $\mu$ g and a molecular weight of greater than about 160.

According to another aspect of the present invention there is provided a use of a physiological cooling agent for the manufacture of a composition for reducing the feeling of numbness associated with anaesthesia wherein the physiological cooling agent comprises one or more cooling agents

having a threshold cooling value of less than about  $100\mu\text{g}$  and a molecular weight of greater than about 160.

All percentages and ratios herein are by weight unless otherwise specified.

### Detailed Description of the Invention

The compositions herein contain, as essential ingredients, a pharmaceutically-acceptable local anaesthetic, a physiological cooling agent and a carrier.

Suitable pharmaceutically-acceptable local anaesthetics for use herein include benzocaine, methyl paraben, benzyl alcohol, salicyl alcohol, phenol, propyl paraben, lignocaine hydrochloride, dyclonine hydrochloride and hexylresorcinol. Preferably the anaesthetic is selected from amide and ester type anaesthetics. More preferably the anaesthetic is selected from benzocaine and lignocaine hydrochloride, most preferably lignocaine hydrochloride. The anaesthetic is preferably present in an amount of from about 0.01 % to about 1 %, more preferably from about 0.02 % to about 0.5 %, most preferably from about 0.05 % to about 0.2 % by weight of composition.

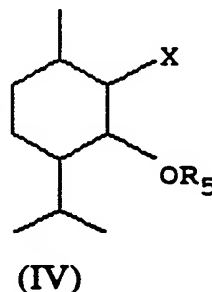
The physiological cooling agent herein comprises one or more cooling agents having a threshold cooling value of at least about  $100\mu\text{g}$  and a molecular weight of greater than about 160. Preferably the cooling agent is selected from carboxamides, menthane esters and menthane ethers, and mixtures thereof, these being preferred from the viewpoint of providing optimum anaesthetic, numbing-suppression and consumer acceptability. According to a further aspect of the invention, there is provided a composition for application to or consumption by the human body comprising:

- i) from about 0.01 % to about 1 % by weight of composition of a pharmaceutically-acceptable local anaesthetic,

- ii) from about 0.01 % to about 1 % by weight of composition of a physiological cooling agent, and,
- iii) a carrier,

wherein the physiological cooling agent comprises one or more cooling agents selected from carboxamides, menthane esters and menthane ethers, and mixtures thereof.

Suitable menthane ethers for use herein are selected from those with the formula:

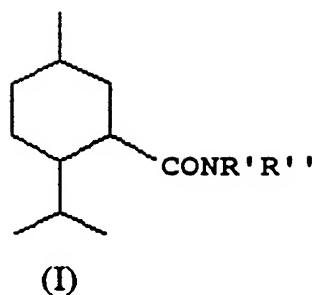


where  $R_5$  is an optionally hydroxy substituted aliphatic radical containing up to 25 carbon atoms, preferably up to 5 carbon atoms, and where X is hydrogen or hydroxy, such as those commercially available under the trade name Takasago, from Takasago International Corporation. A particularly preferred cooling agent for use in the compositions of the present invention is Takasago 10 [3-l-menthoxy propan-1,2-diol (MPD)]. MPD is a monoglycerin derivative of l-menthol and has excellent cooling activity.

The carboxamides found most useful are those described in US-A-4,136,163, January 23, 1979 to Wason et al., and US-A-4,230, 688, October 28, 1980 to Rawsell et al.

The carboxamides in US-A-4,136,163 are N-substituted-p-menthane-3-carboxamides. These compounds are 3-substituted-p-menthanes of the formula:





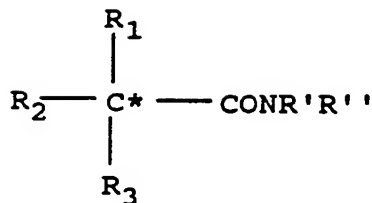
where R', when taken separately, is hydrogen or an aliphatic radical containing up to 25 carbon atoms; R" when taken separately is hydroxy, or an aliphatic radical containing up to 25 carbon atoms, with the proviso that when R' is hydrogen R" may also be an aryl radical of up to 10 carbon atoms and selected from the group consisting of substituted phenyl, phenalkyl or substituted phenalkyl, naphthyl and substituted naphthyl, pyridyl; and R' and R", when taken together with the nitrogen atom to which they are attached, represent a cyclic or heterocyclic group of up to 25 carbon atoms, e.g. piperidino, morpholino etc.

In the above definitions "aliphatic" is intended to include any straight-chained, branched-chained or cyclic radical free or aromatic unsaturation, and thus embraces alkyl, cycloalkyl, alkenyl, cyclo-alkenyl, alkynyl, hydroxyalkyl, acyloxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, acylaminoalkyl, carboxyalkyl and similar combinations.

Typical values for R' and R" when aliphatic are methyl, ethyl, propyl, butyl, isobutyl, n-decyl, cyclopropyl, cyclohexyl, cyclopentyl, cycloheptylmethyl, 2-hydroxyethyl, 3-hydroxy-n-propyl, 6-hydroxy-n-hexyl, 2-aminoethyl, 2-acetoxyethyl, 2-ethylcarboxyethyl, 4-hydroxybut-2-ynyl, carboxymethyl etc.

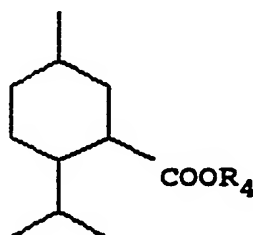
When R" is aryl typical values are benzyl, naphthyl, 4-methoxyphenyl, 4-hydroxyphenyl, 4-methylphenyl, 3-hydroxy-4-methylphenyl, 4-fluorophenyl, 4-nitrophenyl, 2-hydroxynaphthyl, pyridyl, etc.

The carboxamides of US-A-4,230,688 are certain acyclic tertiary and secondary carboxamides. These have the structure



where R' and R'', when taken separately, are each hydrogen, C<sub>1</sub>-C<sub>5</sub> alkyl or C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl and provide a total of no more than 8 carbon atoms, with the proviso that when R' is hydrogen R'' may also be alkylcarboxyalkyl of up to 6 carbon atoms; R' and R'', when taken together, represent an alkylene group of up to 6 carbon atoms, the opposite ends of which group are attached to the amide nitrogen atom thereby to form a nitrogen heterocycle, the carbon chain of which may optionally be interrupted by oxygen; R<sub>1</sub> is hydrogen or C<sub>1</sub>-C<sub>5</sub> alkyl; and R<sub>2</sub> and R<sub>3</sub> are each C<sub>1</sub>-C<sub>5</sub> alkyl; with the provisos that (i) R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> together provide a total of at least 5 carbon atoms, preferably from 5-10 carbon atoms; and (ii) when R<sub>1</sub> is hydrogen, R<sub>2</sub> is C<sub>2</sub>-C<sub>5</sub> alkyl and R<sub>3</sub> is C<sub>3</sub>-C<sub>5</sub> alkyl and at least one of R<sub>2</sub> and R<sub>3</sub> is branched, preferably in an alpha or beta position relative to the carbon atom marked (\*) in the formula.

Suitable menthane esters for use herein are selected from those with the formula:



(III)

where R<sub>4</sub> is hydrogen, hydroxy or an aliphatic radical containing up to 25 carbon atoms.

The physiological cooling agent is preferably present in an amount of from about 0.01 % to about 1 %, more preferably from about 0.02 % to about 0.5 %, most preferably from about 0.05 % to about 0.1 % by weight of composition. Highly preferred cooling agents herein have a threshold cooling value less than that of 1-menthol.

The compositions of the present invention also comprise a carrier. The carrier is chosen according to the particular form the compositions take. The compositions herein are preferably in the form of lozenges or tablets. In the case of lozenges or tablets, the carrier is a sugar or sugar-free base. Sugar-free lozenge compositions are substantially free of saccharose components such as sucrose, fructose etc. while the sugar-based lozenge compositions contain a natural sugar such as sucrose, glucose, fructose, high fructose corn syrup and invert sugar.

Both sugar-free lozenge compositions and sugar-based lozenge compositions can contain one or more sugar alcohols and can be supplemented by conventional candy ingredients such as one or more flavouring agents, colouring agents and/or artificial sweetening agents. Suitable sugar alcohols herein include sorbitol, mannitol, xylitol, maltitol and hydrogenated starch and glucose syrups produced by catalytic hydrogenation of carbohydrate syrups to the point where all carbohydrate end groups are reduced to alcohols. A suitable hydrogenated starch hydrolysate includes from about 5 % to about 10 % sorbitol, from about 25 % to about 75 % maltitol and from about 20 % to about 40 % hydrogenated higher saccharides. Typical hydrogenated starch hydrolysates are Lycasin (RTM) or Maltidex (RTM) 100. Candy compositions can contain up to about 95 % natural sugar and/or sugar alcohol, especially maltitol, sorbitol, mixtures of sorbitol and maltitol, mannitol or other sugar alcohols.

The compositions can additionally comprise menthol in an amount of from about 0.01 % to about 10 %, preferably from about 0.02 % to 0.5 %, by weight.

The compositions can also contain other ingredients such as colouring agents, flavouring agents, preservatives and/or artificial sweetening agents, in order to provide a palatable preparation.

Suitable flavouring agents include synthetic flavour oils and/or oils derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Representative flavour oils include spearmint oil, cinnamon oil, oil of wintergreen (methylsalicylate), eucalyptus and peppermint oils. Also useful are artificial, natural or synthetic fruit flavours such as citrus oil including lemon, orange, grape, lime and grapefruit, and fruit essences including apple, strawberry, cherry, blackcurrent, pineapple and so forth.

The amount of flavouring agents and/or flavour enhancers employed is normally a matter of preference subject to such factors as flavour type, base type and strength desired. In general, amounts of about 0.05% to about 3.0% by weight of final composition are useable with amounts of about 0.3% to about 1.5% being preferred and about 0.7% to about 1.2% being more preferred.

Similarly, artificial sweeteners well-known in the art can be added to the compositions of the invention. Suitable artificial sweeteners encompass water-soluble sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, such as the sodium salt and the like, and the free acid form of saccharin; dipeptide based sweeteners such as L-aspartyl-L-phenylalanine methyl ester and materials described in US-A-3,392,131; dihydrochalcone; glycyrrhizin Stevia rebaudiana (Stevioside); and the synthetic sweetener 3,6-dihydro-6-methyl-1,1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium (Acesulfame-K), sodium and calcium salts thereof as described in DE-A-2,001,017.

Artificial sweeteners are generally used in amounts of from about 0.005% to about 5% and most preferably from about 0.05% to about 1% by weight of the final composition.

Colouring agents can be added to the compositions. Suitable colouring agents include FD&C (Food, Drug & Cosmetic) dyes such as Blue #1 or

#2, FD&C Red #3 plus #40, FD&C Yellow #5 or #6, titanium dioxide or blends of these dyes selected to produce the desired colours.

Alternatively, natural colours such as cermine annatto beta carotene, turmeric, beet, grape skin extract, caramel, and blends thereof may be used as the colourant. Typical use levels for the colouring agent range from 0.01 to 0.03% for synthetic dyes with levels of from 0.1 to 1.0% for the natural colourants.

In addition, organic acids such as citric, malic, maleic, fumaric, succinic, adipic and tartaric acids can be added to lozenge formulations for the purpose of providing tartness.

The compositions of the invention can additionally comprise one or more pharmaceutically-acceptable drugs.

Examples of such drugs include antipyretic and analgesic agents, antiphlogistics, antiarrhythmics, hypotensors, vasodilators, anticholinergics, antiarteriosclerotics, agents for circulatory systems, antitussives, expectorants, ulcer preventives, enzyme preparations, anti-malignants, chemotherapeutic agents, antihistamine agents, enzyme preparations, and mouth disinfection agents, steroidal anti-inflammatory agents, non-steroidal anti-inflammatory agent, anti-allergic agents, vasoconstrictors, and mixtures thereof.

The present invention also relates to the use of a physiological cooling agent for the manufacture of a composition for reducing the feeling of numbness associated with anaesthesia wherein the physiological cooling agent comprises one or more cooling agents having a threshold cooling value of less than about 100 $\mu$ g and a molecular weight of greater than about 160.

The present invention further relates to the use of a physiological cooling agent for the manufacture of a composition for reducing the feeling of numbness associated with anaesthesia wherein the physiological cooling agent comprises one or more cooling agents selected from carboxamides, menthane esters and menthane ethers, and mixtures thereof.

For the purpose of the present disclosure the following test procedure can be used as a means to identify compounds having a physiological cooling activity and herein referred to as cold receptor stimulants. This test is intended purely as a means for identifying compounds having a physiological cooling agent activity and useful in the present invention and for giving an indication of the different relative activities of the compounds, as between themselves and as compared with menthol, when applied in particular manner to a particular part of the body. The results are not necessarily indicative of the activity of these compounds in other formulations and other parts of the body where other factors come into play. For example, a controlling factor in the onset of cooling effect, its intensity and longevity will be the rate of penetration of the compounds through the epidermis and this will vary in different locations on the human body. The formulation of actual products according to this invention will therefore be done largely on an empirical basis although the test results and other figures given herein will be useful as a guide, particularly in the formulation of products for oral administration, since the test procedure to be described involves oral application of the compound. A similar test may, of course, be devised for the purposes of measuring the relative activities of the compounds of another area of the body, for example, the face or forearm, and this will be a useful guide in the choice of compounds to be used in preparations for external topical usage.

It will also be noted that the described test procedure is done on a statistical basis. This is necessary since sensitivity to these compounds will vary not only from compound to compound and from one part of the body to another, but also from one individual to another. Tests of this nature are commonly used in the testing of the organoleptic properties e.g. taste and smell of organic and inorganic compounds, see Kirk-Othmer: Encyclopedia of Chemical Technology, 2nd Ed. (1967) Vol. 14, pages 336-344.

The following test procedure is aimed at determining the minimum quantity of the test compound required to product a noticeable cooling

effect in a person of average sensitivity, this minimum quantity being termed the threshold for that particular compound. The tests are carried out on a selected panel of 6 people of median sensitivity to 1-menthol.

To select a test panel of average sensitivity the following procedure is used. Known quantities of 1-menthol in solution in petroleum ether (bp. 40-60) are placed on 5 mm squares of filter paper, whereafter the solvent is allowed to evaporate. A panel of observers is enrolled and asked to place one impregnated square at a time on the tongue and to report on the presence or absence of a cooling effect. The quantity of 1-menthol on each impregnated square is gradually reduced from a value substantially above  $0.25\mu\text{g}$ . per square to substantially below  $0.25\mu\text{g}$ , the precise range being immaterial. Conveniently, one starts with squares containing  $2.0\mu\text{g}$  being half that of the preceding square, i.e. the second test square will contain  $1.0\mu\text{g}$ , the third  $0.5\mu\text{g}$ , and so on. Each quantity is tested on the tongue at least 10 times. In this way, the thresholds to cold receptor stimulus by 1-menthol are determined for each individual of the panel, the threshold for each individual being that amount of 1- menthol for which, in a series of not less than 10 test applications, a cooling effect is reported 50% of the time. Six panel members are now selected whose threshold to 1-menthol is in the range  $0.1\mu\text{g}$  to  $10\mu\text{g}$  and whose average threshold is approximately  $0.25\mu\text{g}$ , this select panel being regarded as the test panel of average sensitivity.

To test the activity of cooling agents, the above procedure is repeated using only the 6 selected panel members of average sensitivity to 1-menthol. The individual thresholds for each test compound on each of the 6 selected panel members are determined and averaged. Those compounds whose average threshold on the select test panel is  $100\mu\text{g}$  or less are regarded as having cooling activity in accordance with this invention.

The compositions of the present invention are illustrated by the following Examples.

Examples

Lozenges are prepared for the formulation below using conventional hard candy manufacturing equipment.

	I/%	II/%	III/%	IV/%	V/%
Takasago 10 <sup>1</sup>	0.075	0.05	0.1	0.08	0.1
lignocaine hydrochloride	0.09	0.1	0.075	0.1	0.15
menthol	0.25	0.2	-	-	0.25
eucalyptus oil	0.2	0.2	-	0.2	-
colouring agent	0.01	0.01	0.01	0.01	0.01
preservative	0.1	0.05	0.15	0.07	0.1
artificial sweeteners	0.05	0.08	0.1	0.5	0.5
sucrose/glucose (60:40)	----- to 100 -----			-	-
sorbitol/maltitol	-	-	-	--- to 100 ---	

1. Manufactured by Takasago International Corporation; Molecular weight = 230.35; Threshold cooling value = 1/5 that of menthol.

The lozenge compositions of the above examples provide effective anaesthetic activity in the throat while reducing the perceived feeling of numbness associated with the anaesthetic.



### CLAIMS

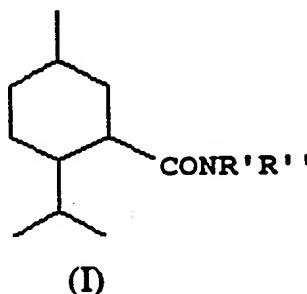
1. A composition for application to or consumption by the human body comprising:
- i) from about 0.01 % to about 1 % by weight of composition of a pharmaceutically-acceptable local anaesthetic,
  - ii) from about 0.01 % to about 1 % by weight of composition of a physiological cooling agent, and,
  - iii) a carrier,

wherein the physiological cooling agent comprises one or more cooling agents having a threshold cooling value of less than about  $100\mu\text{g}$  and a molecular weight of greater than about 160.

2. A composition for application to or consumption by the human body comprising:
- i) from about 0.01 % to about 1 % by weight of composition of a pharmaceutically-acceptable local anaesthetic,
  - ii) from about 0.01 % to about 1 % by weight of composition of a physiological cooling agent, and,
  - iii) a carrier,

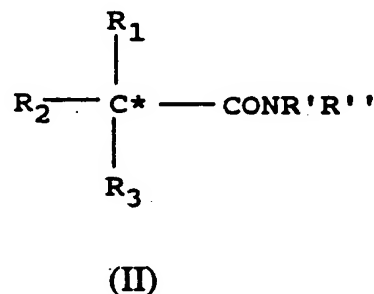
wherein the physiological cooling agent comprises one or more cooling agents selected from carboxamides, menthane esters and menthane ethers, and mixtures thereof.

3. A composition according to Claims 1 or 2 wherein the cooling agent is selected from carboxamides of the formula:



where R', when taken separately, is hydrogen or an aliphatic radical containing up to 25 carbon atoms; R" when taken separately is hydroxy, or an aliphatic radical containing up to 25 carbon atoms, with the proviso that when R' is hydrogen R" may also be an aryl radical of up to 10 carbon atoms and selected from the group consisting of substituted phenyl, phenalkyl or substituted phenalkyl, naphthyl and substituted naphthyl, pyridyl; and R' and R", when taken together with the nitrogen atom to which they are attached, represent a cyclic or heterocyclic group of up to 25 carbon atoms;

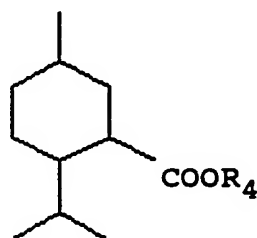
acyclic tertiary and secondary carboxamides of the formula:



where R' and R", when taken separately, are each hydrogen, C<sub>1</sub>-C<sub>5</sub> alkyl or C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl and provide a total of no more than 8 carbon atoms, with the proviso that when R' is hydrogen R" may also be alkylcarboxyalkyl of up to 6 carbon atoms; R' and R", when taken together, represent an alkylene group of up to 6 carbon atoms, the opposite ends of which group are attached to the amide nitrogen atom thereby to form a nitrogen heterocycle, the carbon chain of which may optionally be interrupted by oxygen; R<sub>1</sub> is hydrogen or C<sub>1</sub>-C<sub>5</sub> alkyl; and R<sub>2</sub> and R<sub>3</sub> are each C<sub>1</sub>-C<sub>5</sub> alkyl; with the provisos that (i) R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> together provide a total of at least 5 carbon atoms, preferably from 5-10 carbon atoms; and (ii) when R<sub>1</sub> is hydrogen, R<sub>2</sub> is C<sub>2</sub>-C<sub>5</sub> alkyl and R<sub>3</sub> is C<sub>3</sub>-C<sub>5</sub> alkyl and at least one of R<sub>2</sub> and R<sub>3</sub> is branched, preferably in an

alpha or beta position relative to the carbon atom marked (\*) in the formula; and mixtures thereof.

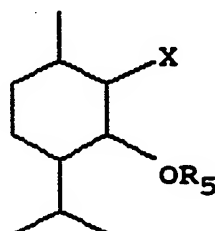
4. A composition according to Claims 1 or 2 wherein the cooling agent is selected from menthane esters of the formula:



(III)

where  $R_4$  is hydrogen, hydroxy or an aliphatic radical containing up to 25 carbon atoms.

5. A composition according to Claim 1 or 2 wherein the cooling agent is selected from menthane ethers of the formula:



(IV)

where  $R_5$  is an optionally hydroxy substituted aliphatic radical containing up to 25, preferably up to 5 carbon atoms and where X is hydrogen or hydroxy.

6. A composition according to Claim 5 wherein the cooling agent is preferably 3-l-menthoxy propan-1,2-diol.

7. A composition according to any of Claims 1 to 6 wherein the local anaesthetic is selected from an amide or an ester type anaesthetic.
8. A composition according to Claim 7 wherein the local anaesthetic is selected from benzocaine and lignocaine hydrochloride, and mixtures thereof.
9. A composition according to Claim 8 wherein the local anaesthetic is lignocaine hydrochloride.
10. A composition according to any of Claims 1 to 9 comprising from about 0.02% to about 0.5% by weight of composition of local anaesthetic.
11. A composition according to any of Claims 1 to 10 comprising from about 0.02% to about 0.5% by weight of composition of physiological cooling agent.
12. A composition according to any of Claims 1 to 11 additionally comprising from about 0.01% to about 10% of menthol.
13. A composition according to any of Claims 1 to 12 wherein the composition is in the form of a lozenge or tablet.
14. A composition according to any of Claim 1 to 13 wherein the composition is a confectionery or pharmaceutical composition.
15. Use of a physiological cooling agent for the manufacture of a composition for reducing the feeling of numbness associated with anaesthesia wherein the physiological cooling agent comprises one or more cooling agents having a threshold cooling value of less than about 100 $\mu$ g and a molecular weight of greater than about 160.
16. Use of a physiological cooling agent for the manufacture of a composition for reducing the feeling of numbness associated with anaesthesia wherein the physiological cooling agent comprises one

or more cooling agents selected from carboxamides, menthane esters and menthane ethers, and mixtures thereof.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US93/08957

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) : A61J 31/435, 31/445, 31/24, 31/22, 31/23, 31/16, 31/075

US CL : 514/277, 315, 535, 546, 552, 613, 715

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/277, 315, 535, 546, 552, 613, 715

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 3,991,178 (Humbert et al.) 09 November 1976, see column 1, lines 7-91.	1, 2, 4
Y	US, A, 4,136,163 (Watson et al.) 23 January 1979, see column 2, lines 7-11 and 29-57.	1, 2, 3
Y	US, A, 4,230,688 (Rowsell et al.) 28 October 1980, see column 1, line 38- column 2, line 23.	1, 2, 3
Y	US, A, 4,459,425 (Amano et al.) 10 July 1984, see column 1, lines 21-43.	1-3, 5, 6
Y	"Physician's Desk Reference for nonprescription Drugs", published 1985 by Edward R. Barnhart, see pp. 607 and 672.	1-6

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

02 November 1993

Date of mailing of the international search report

NOV 12 1993

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## INTERNATIONAL SEARCH REPORT

Inte...ational application No.  
PCT/US93/08957

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>"Handbook of Nonprescription Drugs, 8<sup>th</sup> edition, published 1986 by Am. Pharm. Asso. (Wash., D.C.), pp.162-164, see the preparations marked with an asterisk.</p>	1-6